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C2V 9
C3S 3D 7A

(19)

(54) ALIPHATIC CARBONYL COMPOUNDS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to aliphatic carbonyl compounds. More particularly, the invention is concerned with aliphatic carbonyl compounds and a process for the manufacture thereof.

The aliphatic carbonyl compounds provided by the present invention have the following general formula

(I)

wherein R_1 represents a hydrogen atom or a lower alkoxy, tris(lower alkyl)-silyloxy or di(lower alkyl)amino group, n stands for zero or 1 and the broken lines denotes an optional carbon-carbon bond.

As used herein, the term lower alkyl groups refers to hydrocarbon groups which can be straight-chain or branched-chain, and contain up to 7 carbon atoms. Examples of such groups are the methyl, ethyl, propyl and isopropyl groups.

The term lower alkoxy groups likewise refers to groups containing up to 7 carbon atoms such as the methoxy, ethoxy, propoxy and isopropoxy groups.

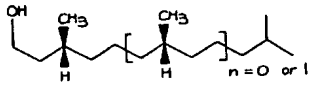
The halogen atom referred to hereinafter can be a fluorine, chlorine, bromine or iodine atom.

The alkali metal referred to hereinafter and denoted by Me is sodium, potassium or lithium.

The term "cis", or the designation Δ, denotes that the two largest groups attached to the double-bond are present on the same side of the double-bond. The term "trans", or the designation Δ', denotes that the two largest groups attached to the double-bond are present on opposite sides of the double-bond.

The designation ▼ denotes that the hydrogen atom or substituent attached in place thereof stands above the plane of the paper.

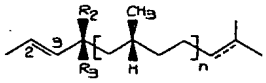
The aliphatic carbonyl compounds of formula I are key intermediates in the synthesis of optically active C_{10}- and C_{15}-alcohols of the following general formula



(X)

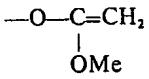
which may be condensed in the manner more precisely described hereinafter with an appropriate optically active chromane component to give the natural optically active 2R,4'R,8'R α-tocopherol.

According to the process provided by the present invention, the aliphatic carbonyl compounds of formula I hereinbefore are manufactured by reacting a pure optically active isomer [free from other optically active isomers] of the general formula

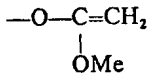


(II)

, wherein n and the broken line have the significance given earlier and one of R_2 and R_3 represents a hydrogen atom and the other represents the hydroxy group or the

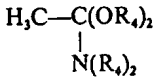


group [Me = alkali metal]; the 2,3-double bond having the cis configuration when R_2 represents the hydroxy group or the

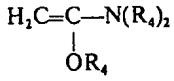


group and having the trans configuration when R_2 represents a hydrogen atom,

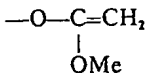
with an orthoacetic acid ester of the formula $H_3C—C(OR_4)_3$ [R_4 = lower alkyl], a ketalised N-dialkyl-acetamide of the formula



an alkoxy-vinyl-dialkylamine of the formula

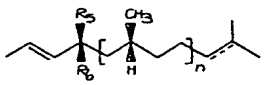


or an alkyl-vinyl ether of the formula $H_2C=CH—OR_4$ when R_2 or R_3 represents the hydroxy group; or with a trialkyl-silyl halide of the formula $XSi(R_4)_3$ [X = halogen) when R_2 or R_3 represents the



group, and subjecting the intermediate obtained to a Claisen rearrangement.

The conversion of the starting materials of formula II into the aliphatic carbonyl compounds of formula I proceeds via a vinyl ether of the general formula



(III)

wherein n and the broken line have the significance given earlier and one of R_5 and R_6 represents a hydrogen atom and the other represents a

$H_2C{=}C(OR_4){-}O{-}$ $H_2C{=}C(N(R_4)_2){-}O{-}$ $H_2C{=}CH{-}O{-}$ or $H_2C{=}C(OSi(R_4)_3){-}O{-}$ group.

It is known that an asymmetric carbon atom is induced in the Claisen rearrangement [see Hill et al. J. Org. Chem. 37 (1972), 3737—3740; Sucrow et al. Chem, Ber. 104 (1971), 3689—3703, Sucrow/Richter Chem. Ber. 104 (1971), 3679—3688]. Thus, in the Claisen rearrangement described by Hill the induction of an asymmetric carbon atom depends on whether an asymmetric carbon atom is already present in the starting material. In accordance with this and according to the present invention, in order to obtain the desired isomer of formula I by the induction of an asymmetric carbon atom there must already be present in the starting material of formula II not only the correct optical configuration of the asymmetric carbon atom, but also the correct geometrical configuration of the double-bond.

If there is used a mixture of the optical and/or geometrical isomers of the starting material of formula II, then there is not obtained in the course of the Claisen rearrangement the desired asymmetric induction of the carbon atom which is necessary for the manufacture of the desired isomer of formula I. It is thus of paramount importance that the starting material of formula II is present in the form of a pure optically active cis- or trans-isomer which is not contaminated by other optically active isomers.

The Claisen rearrangement can be carried out under conditions described in the literature.

If an alkyl-vinyl ether of the formula $H_2C{=}CH{-}OR_4$ is used for the reaction with an optically active isomer of formula II in order to obtain a vinyl ether of formula III which is capable of undergoing the Claisen rearrangement then the reaction is preferably carried out at a temperature between 40°C and 150°C. The reaction is carried out in the presence of a customary acidic catalyst, of which inorganic acids (e.g. phosphoric acid or a hydrohalic acid) as well as salts of acids (e.g. mercuric acetate) are preferred. Organic acid catalysts (e.g. p-toluene-sulphonic acid and p-nitrophenol) can be used. The reaction can be carried out in an inert organic solvent boiling at above 40°C. Preferred inert organic solvents are high-boiling hydrocarbons such as benzene, toluene, xylene and heptane, dimethoxyethane, diethyleneglycol dimethyl ether and dioxane. The resulting vinyl ether intermediate of formula III in which one of R_5 and R_6 represents a hydrogen atom and the other represents the $H_2C{=}CH{-}O{-}$ group can be converted into the desired aldehyde of formula I in which R_1 represents a hydrogen atom by simple heating at 80°C to 200°C.

If an orthoacetic acid ester of the formula $H_3C{-}C(OR_4)_3$ is used for the reaction with an optically active isomer of formula II, an intermediate of formula III in which one of R_5 and R_6 represents a hydrogen atom and the other represents a

$$H_2C{=}C(OR_4){-}O{-}$$

group is formed initially under the reaction conditions customarily used in the Claisen rearrangement.

The reaction is generally carried out using an excess of the orthoacetic acid ester at a temperature between 140°C and 250°C. The orthoacetic acid ester can assume the function of the solvent in this reaction. The reaction can, however, also be carried out in an inert organic solvent which boils at above 140°C. A lower alkanecarboxylic acid is preferably added to the reaction mixture in a molar amount of about 1—10% per mol of the starting material of formula II. In this manner there is obtained an alkyl ester of an optically active isomer of formula I in which R_1 represents an alkoxy group.

If an optically active isomer of formula II is reacted with a trialkyl-sillyl halide of the formula $XSi(R_4)_3$, under conditions for effecting the Claisen rearrangement, then there is first obtained an intermediate of formula III in which one of R_5 and R_6 represents a hydrogen atom and the other represents a

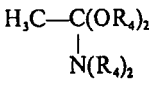
$$H_2C{=}C(OSi(R_4)_3){-}O{-}$$

group. The required starting material is expediently prepared by reacting a compound of formula II in which one of R_2 and R_3 represents a hydrogen atom and the other represents the hydroxy group with a reactive acetic acid derivative (e.g. a halogenated acetic acid or acetic anhydride), enolising the resulting acetal with the aid of an alkali metal alkylamide, the alkyl group of which can comprise a lower alkyl group and/or a cycloalkyl group containing 5—7 carbon atoms, preferably lithium isopropyl cyclohexylamide or lithium diisopropylamide.

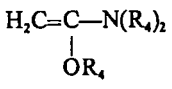
The reaction conditions customary in Claisen rearrangements are used in this reaction. The reaction is preferably carried out in an inert organic solvent and at a temperature between −10°C and −110°C. Any inert organic solvent which does not freeze in the aforementioned temperature range can be used, the preferred solvents being tetrahydrofuran and diethyl ether.

The conversion of the vinyl ether intermediate of formula III into the desired silyl ester of formula I is carried out by simple warming of the reaction mixture to 0°—40°C. The vinyl ether intermediate of formula III need not be isolated, but can be converted in situ into the silyl ester. The vinyl ether intermediate of formula III can, however, also be isolated and then converted by warming into the desired optically active isomeric silyl ester of formula I in which the R_1 represents a tri(lower alkyl)-silyloxy group.

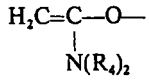
If a ketalised N-dialkylacetamide of the formula



or an alkoxy-vinyl-dialkylamine of the formula

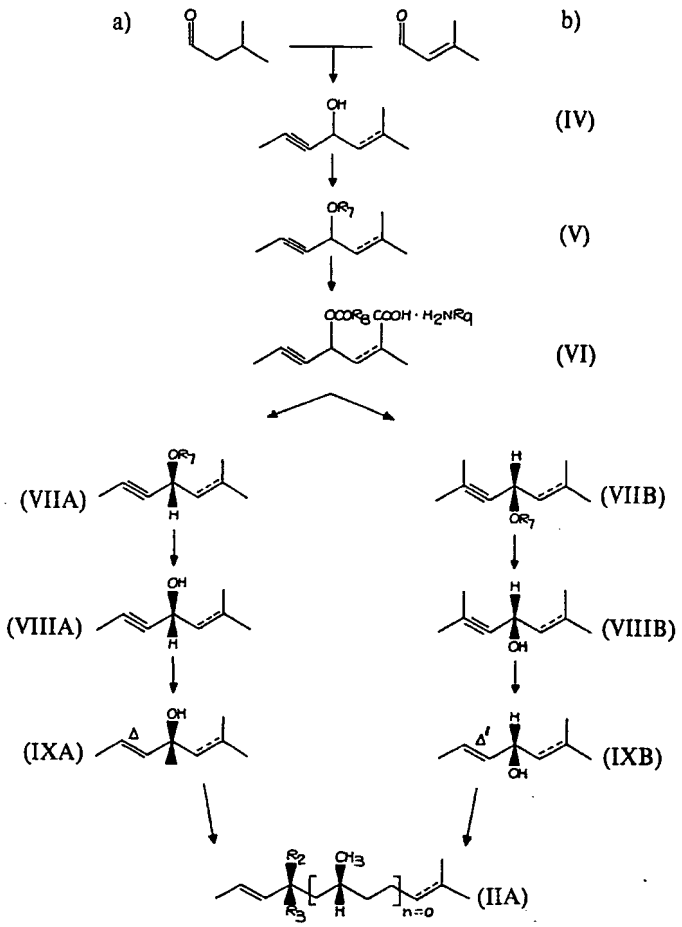


is reacted with an optically active isomer of formula II, then the reaction can be carried out under conditions which are customary in Claisen rearrangements. The resulting vinyl ether intermediate of formula III in which one of R_5 and R_6 represents a hydrogen atom and the other represents the



group is converted directly into the desired amide of formula I. The reaction is carried out at a temperature between 120°C and 250°C and in an inert organic solvent which boils at above 120°C (e.g. xylene or diethyleneglycol dimethyl ether). There is obtained an optically active isomeric dialkylamide of formula I in which R_1 represents a di(lower alkyl)amino group.

The enantiomeric alcohol starting materials of formula II in which n stands for zero [IIA] can be prepared, for example, starting from a) isovaleraldehyde or b) prenal via the conventional steps shown in the following Formula Scheme in which R_2, R_3, n and the broken lines have the significance given earlier, R_7 represents the radical of a dicarboxylic acid, R_8 represents a divalent phenylene or lower alkylene radical and R_9 represents an optically active organic radical:



The conversion of isovaleraldehyde a) or prenal b) into an acetylene derivative of formula IV is carried out by the addition of a methyl-ethynylene-magnesium halide under the conditions of a Grignard reaction.

The resulting acetylene derivative of formula IV must then be separated into the optical antipodes of formulae VIIIA and VIIIB. This can be carried out by reacting said acetylene derivative of formula IV with a dicarboxylic acid to give a hemi-ester of formula V, reacting the hemi-ester of formula V with an optically active base and separating the crystallised enantiomer from the enantiomer remaining in solution.

Examples of dicarboxylic acids which can be used are lower alkanedicarboxylic acids such as oxalic acid, malonic acid, succinic acid, glutamic acid or adipic acid and aromatic dicarboxylic acids such as benzenedicarboxylic acids (e.g. phthalic acid). The esterification is carried out under the customary conditions in the presence of an organic base (e.g. pyridine or an alkylamine).

Of the optically active organic bases which can be used there may be mentioned, for example, brucine, ephedrine and quinine as well as dehydroabietylamine, α-methylbenzylamine and α-methyl-p-nitro-benzylamine. The reaction is carried out under the customary conditions in the presence of an inert organic solvent such as diethyl ether, dioxane, diethyleneglycol dimethyl ether or tetrahydrofuran. When, for example, S-(–)-α-methyl-benzylamine is used as the base, then there is obtained the salt of the hemi-ester of formula VI which has the same absolute configuration and which is crystallised from the solution and separated. The enantiomer remaining in solution can be reacted with the antipode of this base, i.e. with (R)-(+)-α-methyl-benzylamine in the same manner to give the

salt of the enantiomeric hemi-ester, which is likewise crystallised from the solution and separated.

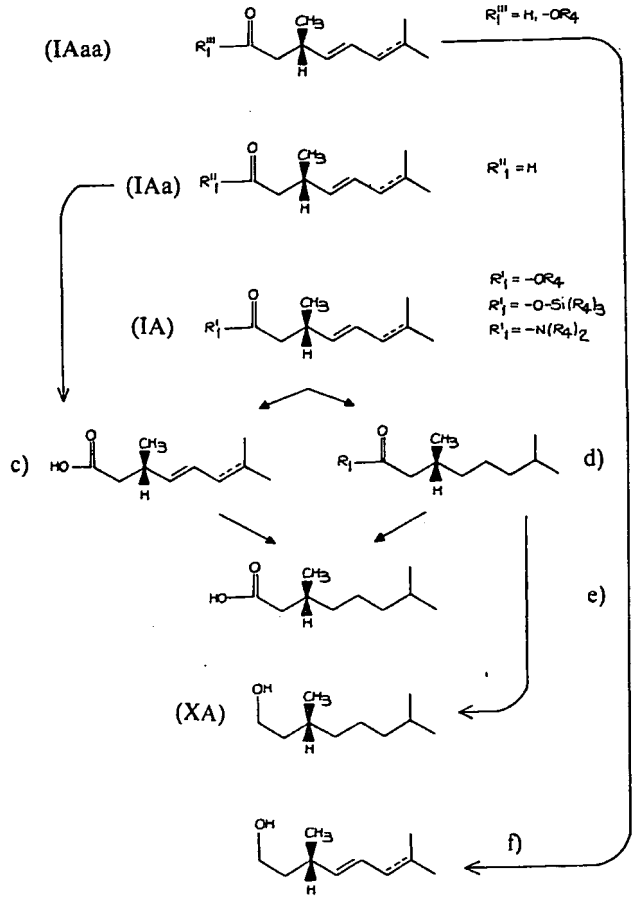
A resulting enantiomeric salt of formula VI is subsequently converted by acidification to pH 0.1 to 4 (e.g. by the addition of an inorganic acid such as sulphuric acid or phosphoric acid or a hydrohalic acid such as hydrochloric acid) into an enantiomeric hemi-ester of formula VIIA or VIIB which is converted into an enantiomeric alcohol of formula VIIIA or VIIIB by hydrolysis, expediently by treatment with an alkali metal base.

A tri-unsaturated alcohol of formula VIIIA or VIIIB is converted into a di-unsaturated alcohol of formula IXA or IXB by partial hydrogenation. The ethynylene group of an alcohol of formula VIIIA is hydrogenated with a partially deactivated palladium catalyst (e.g. a Lindlar catalyst). By this means, an alcohol of formula IXA in which the 2,3-double bond has the cis-configuration is selectively formed.

If, on the other hand, the ethynylene group of an alcohol of formula VIIIB is reduced in a chemical manner (e.g. with sodium in liquid ammonia or with aluminium hydride), then an alcohol of formula IXB in which the 2,3-double bond has the trans-configuration is selectively formed.

The two enantiomeric alcohols of formula IXA and IXB can be generically formulated as in formula II in which n stands for zero [IIA].

The enantiomeric aliphatic carbonyl compounds of formula I in which n stands for zero [IA] can be converted into the aforementioned optically active C_{10}-alcohol of formula X in which n stands for O [XA] as shown, for example, in the following Formula Scheme:



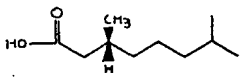
An ester or an amide of formula IA is saponified to the carboxylic acid c) in a conventional manner. An aldehyde of formula IAaa is oxidised to a carboxylic

acid c) in the usual manner; for example, by treatment with manganese dioxide, silver oxide or chromium oxide. The unsaturated carboxylic acid c) obtained from Ia or IAa is hydrogenated in the usual manner with the aid of a metal catalyst (e.g. palladium, platinum or Raney-nickel). The resulting saturated carboxylic acid e) is subsequently reduced to the optically active C_{10}-alcohol of formula XA in a manner known per se with a complex aluminium hydride (e.g. lithium aluminium hydride).

Alternatively, an ester or an amide of formula IA is first hydrogenated as previously described. The resulting saturated ester or an amide d) is then saponified to the saturated carboxylic acid e) which, as previously described, is reduced to the optically active C_{10}-alcohol of formula XA. An ester or an amide d) can also be directly reduced in a procedure involving concomitant saponification to give the desired optically active C_{10}-alcohol of formula XA.

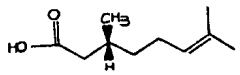
A carboxylic acid ester or aldehyde of formula IAàa can be directly reduced to the unsaturated alcohol f) which can subsequently be hydrogenated to give the optically active C_{10}-alcohol of formula XA.

The diastereomeric alcohol starting materials of formula II in which n stands for 1 [IIB] can be prepared, for example, from the previously described carboxylic acid of the formula



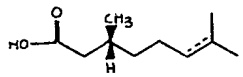
e) (XVI)

or from the known unsaturated carboxylic acid of the formula



e').

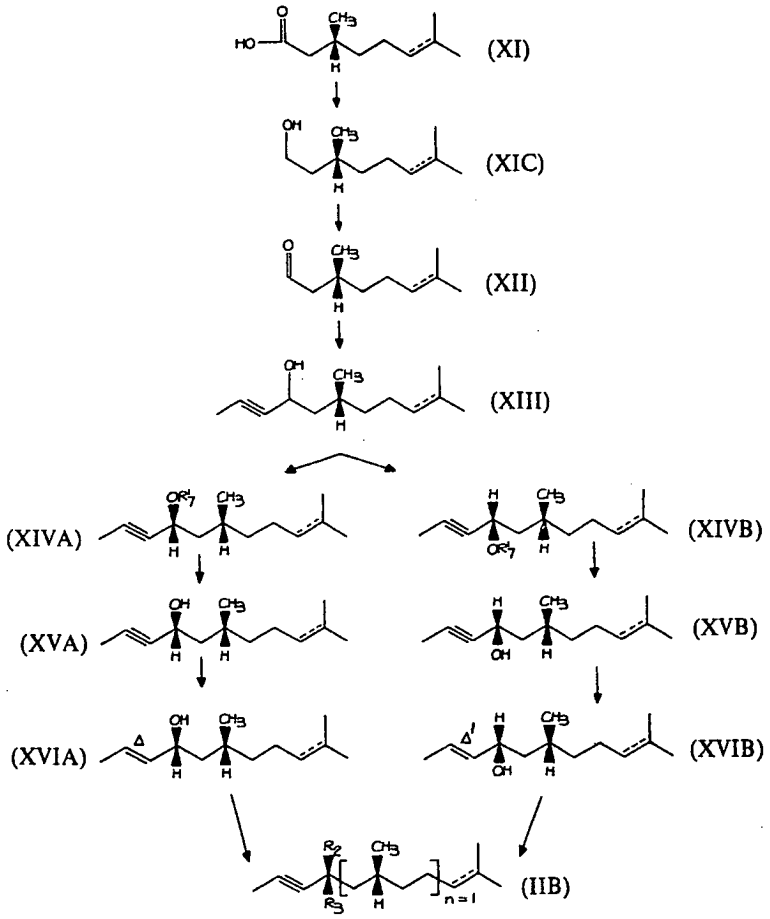
Such acids can be generically formulated thus



(XI)

wherein the broken line has the significance given earlier.

The preparation of the starting materials of formula IIB from these acids via the conventional steps shown in the following Formula Scheme in which R'_7 represents a hydrogen atom or an acyl group and R_2, R_3 and the broken line have the significance given earlier:



A carboxylic acid of formula XI is first reduced in a known manner (e.g. with the aid of a complex metal hydride such as lithium aluminium hydride). A resulting alcohol of formula XIc is subsequently oxidised in a conventional manner (e.g. by treatment with chromium oxide, silver carbonate, chlorine in dimethylsulphoxide or dicyclohexylcarbodiimide in dimethylsulphoxide).

A resulting aldehyde of formula XII is reacted with a methyl-ethynylene magnesium halide as described previously in the chain-lengthening of prenal or isovaleraldehyde.

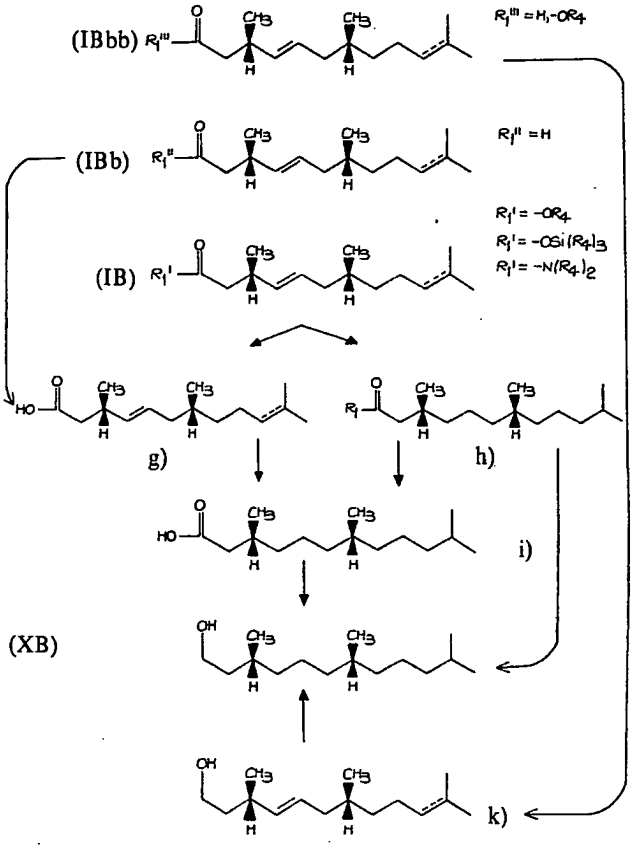
A resulting acetylene derivative of formula XIII is present as a mixture of the two diastereomers in a ratio of 1:1. This mixture can be separated in a manner known per se by chromatography, preferably by column chromatography or high-pressure gas chromatography. It has proved to be expedient to esterify the hydroxy group of the acetylene derivative of formula XIII before carrying out the chromatographic separation. The hydroxy group can be esterified with a lower alkanecarboxylic acid or an arylcarboxylic acid, especially with a phenyl-carboxylic acid or with a phenylcarboxylic acid substituted by amino, nitro, lower alkyl or halogen (e.g. 3,5-dinitrobenzoic acid).

A resulting diastereomer of formula XIVA or XIVB is converted, insofar as it is present as an ester, by hydrolysis into a diastereomeric alcohol of formula XVA or XVB. An alcohol of formula XVA is reduced with the aid of a metal catalyst to a cis-alcohol of formula XVIA as previously described in the partial hydrogenation of a tri-unsaturated alcohol of formula VIIIA to a di-unsaturated alcohol of formula IXA. An alcohol of formula XVB is reduced with the aid of a chemical agent to a trans-alcohol of formula XVIB as previously described in the reduction of an alcohol of formula VIIIB to a an alcohol of formula IXB.

The two diastereomeric alcohols of formulae XVIA and XVIB can be

generically formulated as in formula II in which n stands for 1 [IIB].

The diastereomeric aliphatic carbonyl compounds of formula I in which n stands for 1 [IB] can be converted into the aforementioned optically active C_{15}-alcohol of formula X in which n stands for 1 [XB] as shown, for example, in the following Formula Scheme:



An ester or an amide of formula IB is saponified in a conventional manner to give a carboxylic acid g). An aldehyde of formula IBb is oxidised to a carboxylic acid g) by treatment with, for example, manganese dioxide, silver oxide or chromium oxide. An unsaturated carboxylic acid g) obtained from an ester or amide of formula IB or from an aldehyde of formula IBb is hydrogenated in the usual manner with the aid of a metal catalyst (e.g. palladium, platinum or Raney-nickel). The resulting saturated carboxylic acid i) is subsequently reduced to the optically active C_{15}-alcohol of formula XB in a manner known per se with a complex aluminium hydride (e.g. lithium aluminium hydride).

An ester or an amide of formula IB is first hydrogenated as previously described. A resulting saturated ester or amide h) is then saponified to the saturated carboxylic acid i) which, as described earlier, is reduced to the optically active C_{15}-alcohol of formula XB. A resulting saturated ester or amide h) can also be directly reduced in a procedure involving concomitant saponification to give the desired optically active C_{15}-alcohol of formula XB.

An alkanecarboxylic acid ester or aldehyde of formula IBbb can be reduced to give an unsaturated alcohol k) which can subsequently be hydrogenated to give the optically active C_{15}-alcohol of formula XB.

The optically active alcohols of formula X obtained from the aliphatic carbonyl compounds of formula I can be condensed, as described in Examples 16 and 17, with the appropriate chromane component to give optically active 2R,4'R,8'R-α-tocopherol.

The C_{10}-alcohol of formula XA is converted via the bromide into the C_{10}-magnesium bromide according to Example 16 and reacted with 5-[6-benzyloxy-2(R),5,7,8 - tetramethyl - 2 - chromanyl] - 2(S) - methyl - pentyl - p - toluenesulphonate to give 2R,4'R,8'R-α-tocopherol benzyl ether.

The C_{15}-alcohol of formual XB is converted via the bromide into the C_{15}-triphenylphosphonium bromide according to Example 16 and reacted with 6-acetoxy-2-formyl-2(R),5,7,8-tetramethyl chromane to give 2R,4'R,8'R-1',2'-dehydro-α-tocopherol acetate which is hydrogenated to 2R,4'R,8'R-α-tocopherol acetate.

The following Examples illustrate the present invention:

Example 1.

5.0 g of 6-methyl-2(cis)-hepten-4(R)-ol, 290 mg of propionic acid and 44.5 g of orthoacetic acid ethyl ester are gently heated under reflux in an inert gas atmosphere. The liberated ethanol is distilled off. The mixture is subsequently heated to boiling under reflux at 142°C for 3 hours. The excess orthoacetic acid ethyl ester is then distilled off under reduced pressure. The residue is purified by vacuum distillation. The resulting 3(S),7-dimethyl-4(trans)-octenoic acid ethyl ester, a colourless oil, boils at 66°—67°C/0.9 Torr; $[\alpha]_D^{25} = +19.15°$ (c = 4.882 in chloroform).

The 6-methyl-2(cis)-hepten-4(R)-ol used as the starting material can be prepared, for example, as follows:

a) 143 g of dry methylacetylene are led into a solution of ethylmagnesium bromide (prepared from 78.5 g of magnesium and 338 g of ethyl bromide). The resulting propynylmagnesium bromide is treated dropwise within 60 minutes at 0°C in an inert gas atmosphere with 221 g of distilled isovaleraldehyde. The internal temperature should not rise above 5°C during this treatment. The mixture is stirred for 30 minutes, then slowly introduced while stirring into a solution of 400 g of ammonium chloride in 2 litres of water and extracted with ether. The ether extract is washed three times with water, dried over magnesium sulphate and evaporated under reduced pressure. The residual crude and slighly yellow-coloured 6-methyl-2-heptyn-4(R,S)-ol is purified by distillation. The pure acetylenic alcohol, a colourless oil, boils at 60°C/3 Torr.

b) 220 mg of 6-methyl-2-heptyn-4(R,S)-ol, 265 g of phthalic acid anhydride and 220 ml of dry pyridine are heated to boiling under reflux for 4 hours. The mixture is subsequently cooled to room temperature and shaken out with 500 ml of ether. The ether solution is washed three times with 500 ml of 1-N hydrochloric acid each time and then extracted three times with 500 ml of 1-N ammonium hydroxide each time. The extract is shaken out twice with 500 ml of ether each time, then cooled to 0°C, acidified with concentrated hydrochloric acid up to a Congo-acid reaction and extracted three times with 500 ml of chloroform each time. The chloroform extract is washed with water, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The white (R,S)-6-methyl-2-heptyne-4-phthalic acid monoester which crystallises from the slightly brown-coloured residue after the addition of ethanol, melts at 103°—105°C.

c) 202 g of (R,S)-6-methyl-2-heptyne-4-phthalic acid monoester are dissolved in 3 litres of ether. The solution is treated with 122 g of S-(–)-α-methylbenzylamine. The mixture is stirred at 25°C under nitrogen for 2 hours. The S-α-methylbenzylamine salt of the S-(–)-6-methyl-2-heptyne-4-phthalic acid monoester, which occurs in crystalline form, is filtered off, washed with ether and recrystallised from methanol/ether up to a constant rotation. The salt melts at 125°—130°C; $[\alpha]_D^{25} = -27.39°$ (c = 1.05 in chloroform).

d) A suspension of 102.7 g of the previously obtained hemi-ester salt in 500 ml of 1-N hydrochloric acid is stirred for 1 hour at 25°C and then shaken out with ether. The ether phase is separated and washed with 1-N hydrochloric acid. The aqueous phase is extracted again with ether. The combined ether extracts are washed with water, dried over magnesium sulphate and evaporated under reduced pressure. The residual, slightly yellow-coloured S-(–)-6-methyl-2-heptyne-4-phthalic acid monoester is recrystallised from ethanol/water. The pure white hemi-ester melts at 103°—106°C; $[\alpha]_D^{25} = -8.48°$ (c = 0.990 in ethanol).

e) The mother liquors of the S-α-methylbenzylamine salt of S-(–)-6-methyl-2-heptyne-4-phthalic acid monoester are treated with 1-N hydrochloric acid. The yellowish oil is treated with R-α-methylbenzylamine as described previously. The resulting R-α-methylbenzylamine salt of the R-(+)-6-methyl-2-heptyne-4-phthalic acid monoester melts at 128°—138°C; $[\alpha]_D^{25} = +27.06°$ (c = 1.0 in chloroform).

f) The R-(+)-6-methyl-2-heptyne-4-phthalic acid monoester obtainable from the R-α-methylbenzylamine salt of the R-(+)-6-methyl-2-heptyne-4-phthalic acid monoester by treatment with hydrochloric acid, melts at 105°—109°C; $[\alpha]_D^{25} = +7.81°$ (c = 0.986 in ethanol).

g) After the addition of 500 ml of 2-N sodium hydroxide, 119 g of R-(+)-6-methyl-2-heptyne-4-phthalic acid monoester are heated for 1 hour under reflux, then cooled to room temperature and extracted four times with 150 ml of chloroform each time. The (+)-6-methyl-2-heptyn-4-(R)-ol isolated from the chloroform extract boils at 58°—59°C/1.0 Torr; $[\alpha]_D^{25} = +13.48°$ (c = 1 in chloroform).

h) The (–)-6-methyl-2-heptyn-4(S)-ol obtained in the same manner from S-(–)-6-methyl-2-heptyne-4-phthalic acid monoester boils at 54°—55°C/0.3 Torr; $[\alpha]_D^{25} = -13.02°$ (c = 1 in chloroform).

i) After the addition of 1 ml of quinoline, 25 g of 6-methyl-2-heptyn-4(R)-ol dissolved in 300 ml of n-hexane are hydrogenated under normal conditions with the aid of 2.5 g of Lindlar catalyst [$Pd/CaCO_3/PbO$]. After the uptake of 5.05 litres of hydrogen within 3.5 hours, the hydrogenation is interrupted. The catalyst is filtered off and washed with n-hexane. The combined hexane solutions are evaporated under reduced presure. The residual 6-methyl-2(cis)-hepten-4(R)-ol boils at 48°—49°C/1 Torr; $[\alpha]_D^{25} = +21.02°$ (c = 5.053 in chloroform).

Example 2.

In an analogous manner to that described in Example 1, 9.5 g of 6-methyl-2(trans)-hepten-4(S)-ol are reacted, after the addition of 290 mg of propionic acid, with 44.5 g of orthoacetic acid ethyl ester to give 3(S),7-dimethyl-4(trans)-octenoic acid ethyl ester which boils at 33°—37°C/0.2 Torr; $[\alpha]_D^{25} = +18.42°$ (c = 5.033 in chloroform).

a) The 6-methyl-2(trans)-hepten-4(S)-ol used as the starting compound can be prepared, for example, as follows:

20 g of the 6-methyl-2-heptyn-4(S)-ol obtained according to Example 1h) in 25 ml of dry ether are added dropwise to a sodium amide solution prepared at –78°C from 300 ml of dry ammonia and 11.3 g of sodium metal. The mixture is stirred for 6 hours in a dry-ice/acetone bath, then treated slowly until disappearance of the blue coloration, firstly with 2 g of ammonium chloride and then with 50 ml of a saturated aqueous ammonium chloride solution. The ammonia is gradually distilled off. The solution is extracted with ether. The ether extract is washed first with 1-N hydrochloric acid and then with water, dried over magnesium sulphate and evaporated under reduced pressure. The residual 6-methyl-2(trans)-hepten-4(S)-ol, a colourless oil, boils at 43°—44°C/0.6 Torr.

Example 3.

In an analogous manner to that described in Example 1, 2.0 g of 6-methyl-2(cis)-hepten-4(R)-ol are reacted, after the addition of 20 ml of xylene, with 4.0 g of 1-dimethylamino-1,1-dimethoxyethane to give 3(S),7-dimethyl-4(trans)-octenoic acid dimethylamide, a slightly yellow-coloured oil, which boils at 115°—116°C/1.5 Torr; $[\alpha]_D^{25} = +19.36°$ (c = 5.087 in chloroform).

Example 4.

In the same manner as described in Example 3, 2.0 g of 6-methyl-2(trans)-hepten-4(S)-ol are reacted, after the addition of 20 ml of xylene, with 4.0 g of 1-dimethylamino-1,1-dimethoxyethane to give 3(S),7-dimethyl-4(trans)-octenoic acid dimethylamide which boils at 103°—104°C/0.7 Torr; $[\alpha]_D^{25} = +20.64°$ (c = 5.033 in chloroform).

Example 5.

4.67 ml of n-butyllithium in hexane are treated dropwise with 1.78 ml of N-isopropylcyclohexylamine in 2.0 of anhydrous tetrahydrofuran under argon and in an ice-bath. The hexane is distilled off under anhydrous conditions under reduced pressure. The residue is cooled to –78°C and, after the addition of 3 ml hexamethylphosphoric acid triamide, treated dropwise with 1.702 g of 6-methyl-4(R)-acetoxy-2-(cis)-heptene in 2 ml of tetrahydrofuran. After completion of the addition, the mixture is stirred, for a further 10 minutes. The clear thickish yellow lithium enolate of the 6-methyl-4(R)-acetoxy-2(cis)-heptene is treated with 1.65 g of tert.butyl-dimethyl-chlorosilane in 2 ml of tetrahydrofuran. The mixture is stirred firstly for 10 minutes at –78°C in order to complete the formation of the O-

[R-[6-methyl-2(cis)-hepten-4-yl]]-O'-dimethyl-tert.butyl-silyl-ketene acetal and subsequently for a further 48 hours at room temperature. The clear slightly yellow solution is then introduced into 300 ml of pentane, washed three times with 50 ml of water each time, dried over magnesium sulphate and evaporated under reduced pressure. The residual 3(S),7-dimethyl-4-(trans)-octenoic acid tert.butyl-dimethyl-silyl ester boils at 40°—50°C/0.5 Torr.

Example 6.

In an analogous manner to that described in Example 5, the S-[6-methyl-2(trans)-hepten-4-yl]-O-dimethyl-tert.butyl-silyl-ketene formed from 6-methyl-4(S)-acetoxy-2(trans)-heptene, n-butyllithium and tert.butyl-dimethylchlorosilane is rearranged to give 3(S),7-dimethyl-4(trans)-octenoic acid tert.butyl-dimethyl-silyl ester.

Example 7.

After the addition of 3.5 g of mercuric acetate, 1.5 g of 6-methyl-2(cis)-hepten-4(R)-ol and 15 ml of ethyl-vinyl ether are heated under reflux in an inert gas atmosphere for 21 hours. After a further addition of 5 ml of ethyl-vinyl ether and 40 ml of benzene, the mixture is heated under reflux for a further 4 hours, then cooled to room temperature, treated with 1 ml of glacial acetic acid, stirred for 1 hour and then diluted with ether. The ether solution is washed four times with a 5 wt.% aqueous potassium hydroxide solution, dried over potassium carbonate and evaporated under reduced pressure. The residual 6-methyl-4(R)-vinyloxy-2(cis)-heptene [boiling point 30°—60°C/40 Torr] is dissolved in 100 ml of benzene. The solution is heated to boiling under reflux in an inert gas atmosphere for 120 hours. The solvent is distilled off under reduced pressure. The residual 3(S),7-dimethyl-4(trans)-octenal is purified by adsorption on 25 g of silica gel using ether/petroleum ether (30°—60°C) (1:9) for the elution. The pure cis-aldehyde boils at 36°C/0.5 Torr; $[\alpha]_D^{25} = +30.18°$ (c = 3.572 in chloroform).

Example 8.

In an analogous manner to that described in Example 7, from 6-methyl-2-(trans)-hepten-4(S)-ol and ethyl-vinyl ether there is obtained 3(S),7-dimethyl-4-(trans)-octenal.

Example 9.

After the addition of 30 mg of propionic acid, 1.3 g of 6(R),10-dimethyl-2(trans),9-undecadien-4(S)-ol and 7.54 g of orthoacetic acid ethyl ester are heated under reflux. The liberated ethanol is distilled off. The remaining mixture is heated to boiling under reflux for a further 20 hours and then evaporated under reduced pressure. The residual 3(S),7(R)-11-trimethyl-4(trans),10-dodecadienoic acid ethyl ester boils at 65°C/0.2 Torr; $[\alpha]_D^{25} = +6.53°$ (c = 0.9195 in n-octane).

The 6(R),10-dimethyl-2(trans),9-undecadien-4(S)-ol used as the starting material can be prepared, for example, as follows:

a) 150 g of 3(R),7-dimethyl-6-octen-1-al are dissolved in 200 ml of ether. The solution is added dropwise while stirring at 5°C to a suspension prepared from 133 g of ethyl bromide, 32.9 g of magnesium and 120 g of propyne in 900 ml of ether. The mixture is then heated to room temperature and worked-up as described in Example 1a). The resulting 6(R),10-dimethyl-9-undecen-2-yn-4(R,S)-ol, a colourles oil, boils at 95°C/0.3 Torr. The racemate is separated by adsorption on 2 kg of silica gel [eluant: ether/petroleum ether] into:

6(R),10-dimethyl-9-undecen-2-yn-4(S)-ol; $[\alpha]_D^{25} = -7.83°$ (c = 2.441 in chloroform); and

6(R),10-dimethyl-9-undecen-2-yl-4(R)-ol; $[\alpha]_D^{25} = +9.07°$ (c = 5.038 in chloroform).

b) 2.0 g of 6(R),10-dimethyl-9-undecen-2-yn-4-ol are dissolved in 120 ml of dry ether. The solution is gassed with argon and treated dropwise with a suspension of 3.02 ml of sodium bis-(2-methoxyethoxy)-aluminium hydride in 40 ml of dry ether, the mixture boiling slightly under reflux. After 17 hours under reflux the mixture is heated to boiling, then cooled to 0°C, treated carefully with 20 ml of aqueous sulphuric acid [4:1] and then diluted with 200 ml of water and 200 ml of ether while stirring. The two phases are separated. The aqueous layer is again shaken with ether. The combined ether extracts are washed with a 5% aqueous sodium bicarbonate solution, dried over sodium sulphate and evaporated under reduced

pressure. The residual colourless oily 6(R),10-dimethyl-2(trans)-9-undecadiene-4(S)-ol boils at 58°—60°C/0.2 Torr.

Example 10.

In an analogous manner to that described in Example 9, from 6(R),10-dimethyl-2(cis), 9-undecadien-4(R)-ol and orthoacetic acid ethyl ester there is obtained 3(S),7(R),11-trimethyl-4(trans),10-dodecadienoic acid ethyl ester.

The 6(R),10-dimethyl-2(cis),9-undecadien-4(R)-ol used as the starting material can be prepared, for example, as follows:

a) 1.5 g of 6(R),10-dimethyl-9-undecen-2-yn-4(R)-ol prepared according to Example 9a) are dissolved in 70 ml of n-hexane. After the addition of 0.6 ml of quinoline, the solution is hydrogenated under normal conditions with the aid of 150 mg of Lindlar catalyst [$Pd/CaCO_3/PbO$]. The resulting 6(R),10-dimethyl-2(cis)-9-undecadien-4(R)-ol boils at 48°—60°C/0.7 Torr.

Example 11.

After the addition of 20 ml of xylene, 850 mg of 6(R),10-dimethyl-2(cis)-undecen-4(R)-ol and 2.0 g of 1-dimethylamino-1,1-dimethoxyethane are heated to boiling under reflux for 20 hours. The xylene is then distilled off at 55°C/10 Torr. The residual 3(S),7(R),11-trimethyl-4(trans)-dodecenoic acid dimethylamide, a slightly yellowish oil, boils at 68°—71°C/0.15 Torr.

The 6(R),10-dimethyl-2(cis)-undecen-4(R)-ol used as the starting material can be prepared, for example, as follows:

a) A solution of propynylmagnesium bromide (prepared from 77 g of ethyl bromide, 10.8 g of magnesium and 100 ml of methylacetylene in 400 ml of absolute ether) is treated dropwise at 0°—5°C with a solution of 26.4 g of 3(R),7-dimethyl-octan-1-al [R-(+)-dihydrocitronella] in 500 ml of ether. The mixture is subsequently heated to 30°C, stirred for 1 hour and then treated slowly in an ice-bath with a solution of 100 g of ammonium chloride in 600 ml of water. The aqueous phase is separated and extracted three times with 250 ml of ether each time. The combined ether solutions are filtered, washed three times with 500 ml of sodium chloride solution each time, dried over magnesium sulphate and evaporated under reduced pressure. The residual 6(R),10-dimethyl-undecan-2-yn-4(R,S)-ol, a light amber-coloured oil, is subsequently adsorbed on 3.36 kg of silica gel and separated by elution with ether/petroleum ether (30°—60°C) (10:90) into:

6(R),10-dimethyl-undecan-2-yn-4(S)-ol and

6(R),10-dimethyl-undecan-2-yn-4(R)-ol.

b) 8.25 g of p-toluenesulphonyl chloride in 15 ml of pyridine are introduced portionwise while stirring into a solution of 4.58 g of 3,5-dinitrobenzoic acid in 25 ml of pyridine. The solution is cooled in an ice-bath and treated gradually with 4.22 g of 6(R),10-dimethyl-undecan-2-yn-4(R)-ol in 15 ml of pyridine. In so doing, the internal temperature should not rise above 6°C. The mixture is stirred at 5°C for 20 minutes, then pured into ice-water and extracted four times with 200 ml of chloroform each time. The chloroform extracts are washed successively three times with 200 ml of 2-N hydrochloric acid each time, twice with 200 ml of a saturated aqueous sodium bicarbonate solution each time and once with 200 ml of a sodium chloride solution, dried over magnesium sulphate and evaporated under reduced pressure. The residual 6(R),10-dimethyl-4(R)-dinitrobenzoyloxy-undecan-2-yne melts at 90—91°C after recrystallisation from methanol.

c) After the addition of 35 ml of 6-N sodium hydroxide, 6.65 g of 6(R),10-dimethyl-4(R)-dinitrobenzoyloxy-undecan-2-yne are heated under reflux in 300 ml of methanol for 90 minutes. The methanol is distilled off under reduced pressure. The mixture is diluted with 750 ml of water. The separated aqueous phase is extracted four times with 300 ml of ether each time. The combined ether solutions are washed successively three times with 300 ml of water each time and once with 300 ml of a sodium chloride solution, dried over magnesium sulphate and evaporated under reduced pressure. The residual 6(R),10-dimethyl-undecan-2-yn-4(R)-ol is a colourless oil.

d) After the addition of 0.6 ml of quinoline, 3.2 g of 6(R),10-dimethyl-undecan-2-yn-4(R)-ol are hydrogenated in 120 ml of n-hexane with the aid of 320 mg of Lindlar catalyst [$Pd/CaCO_3/PbO$]. After uptake of 395 ml of hydrogen within 1 hour, the hydrogenation is interrupted. The catalyst is filtered off and washed with 100 ml of n-hexane. The combined hexane solutions are washed successively three times with 30 ml of 1-N sulphuric acid each time, three times with 30 ml of an aqueous saturated sodium bicarbonate solution each time and three times with 30

ml of water each time, dried over magnesium sulphate and evaporated under reduced pressure. The residual 6(R),10-dimethyl-2(cis)-undecen-4(R)-ol, a colourless oil, boils at 102°C/0.2 Torr.

Example 12.

After the addition of 57 mg of propionic acid 2.9 g of 6(R),10-dimethyl-2(cis)-undecen-4(R)-ol and 16.5 g of orthoacetic acid ethyl ester are heated to boiling for 2 hours under reflux. The excess orthoacetic acid ethyl ester is then distilled off at ca 1 Torr. The residual 3(S),7(R),11-trimethyl-4(trans)-dodecenoic acid ethyl ester, a colourless oil, boils at 95°—101°C/0.1 Torr.

Example 13.

In an analogous manner to that described in Example 12, 1.44 g of 6(R),10-dimethyl-2-(trans)-undecen-4(S)-ol and 9.05 of orthoacetic acid ethyl ester are heated under reflux, after the addition of 34 mg of propionic acid, for 105 minutes and worked-up. The resulting 3(S),7(R),11-trimethyl-4(cis)-dodecenoic acid ethyl ester boils at 96°—105°C/0.25 Torr.

The 6(R),10-dimethyl-2(trans)-undecen-4(S)-ol used as the starting material can be prepared, for example, as follows:

a) 4.0 g of the 6(R),10-dimethyl-undecan-2-yn-4(S)-ol obtained according to Example 11a) are reacted as described in Example 11b) with 4.33 g of 3,5-dinitrobenzoic acid in the presence of 7.75 g of p-toluenesulphonyl chloride in 15 ml of pyridine to give 6(R),10-dimethyl-4(S)-dinitrobenzoyloxy-undecan-2-yne which melts at 88°—90.5°C after recrystallisation from methanol.

b) 5.4 g of 6(R),10-dimethyl-4(S)-dinitrobenzoyloxy-undecan-2-yne are converted as described in Example 11c) by treatment with 54 ml of 6-N sodium hydroxide in 250 ml of methanol into 6(R),10-dimethyl-undecan-2-yn-4(S)-ol, a colourless oil, which boils at 87°C/0.175 Torr.

c) 1.9 g of 6(R),10-dimethyl-undecan-2-yn-4(S)-ol are dissolved in 75 ml of dry ether. The solution is treated dropwise with a suspension of 3.02 ml of sodium bis(2-methoxyethoxy)-aluminium hydride in 60 ml of dry ether and worked-up as described in Example 9b). The resulting 6(R),10-dimethyl-2(trans)-undecen-4(S)-ol, a colourless oil, boils at 85°C/1.1 Torr.

Example 14.

The compounds obtained according to the Examples 1—8 can be converted in a manner known per se (e.g. as follows) into the aforementioned, optically active C_{10}-alcohol of formula XA, a side-chain component of α-tocopherol:

a) 500 mg of the 3(S),7-dimethyl-4(trans)-octenal obtained according to Example 7 are dissolved in 10 ml of ethanol. After the addition of 1.1 g of silver nitrate in 20 ml of water, the solution is treated dropwise with 2.17 ml of 6-N sodium hydroxide and stirred for 30 minutes at 23°C. The precipitated dark-coloured sediment is filtered off and washed successively with 15 ml of 0.1-N sodium hydroxide, 15 ml of water and 15 ml of ether. The aqueous phases are combined, washed twice with ether, then cooled to 0°C, made Congo-acid by the addition of concentrated hydrochloric acid and subsequently extracted with ether. The ether phase is washed with water, dried over magnesium sulphate and evaporated under reduced pressure. The residual slightly yellow-coloured 3(S),7-dimethyl-4(trans)-octenoic acid boils at 56°C/0.5 Torr; $[\alpha]_D^{25}$= +27.20° (c=5.1835 in chloroform).

b) 335 mg of 3(S),7-dimethyl-4(trans)-octenoic acid are hydrogenated under normal conditions with the aid of 30 mg of palladium/carbon [5% Pd] in 10 ml of ethyl acetate. The resulting (R)-(+)-dihydrocitronellic acid [3(R),7-dimethyl-octan-1-oic acid] boils at 56°C/0.5 Torr.

c) 564 mg of (R)-(+)-dihydrocitronellic acid are dissolved in 2 ml of absolute ether. The solution is treated with 4.59 ml of sodium bis(2-methoxyethoxy)-aluminium hydride in 5 ml of ether and stirred at 25°C for 17 hours. The mixture is then treated in a dropwise ice-bath with 1 ml of concentrated sulphuric acid. The organic phase is extracted twice with 50 ml of ether each time. The ether extract is washed three times with 50 ml of water each time, dried over magnesium sulphate and evaporated under reduced pressure. The residual (R)-(+)-dihydrocitronellol [3(R),7-dimethyl-octan-1-ol] is a colourless oil; $[\alpha]_D^{25}$= +4.10° (c=4.003 in chloroform).

Example 15.

The compounds obtained according to Examples 9—13 can be converted in a

manner known per se (e.g. as follows) into the aforementioned optically active C_{15}-alcohol of formula XB, a side-chain component of α-tocopherol.

a) 1.13 g of the 3(S),7(R),11-trimethyl-4(trans),10-dodecadienoic acid ethyl ester obtained according to Example 10 are hydrogenated under normal conditions with the aid of 113 mg of palladium/carbon [5% Pd] in 80 ml of ethyl acetate. The resulting 3(R),7(R),11-trimethyl-dodecanoic acid ethyl ester has a rotation value of $[\alpha]_D^{23} = +1.05°$ (c=0.951 in n-octane).

b) After the addition of 500 mg of lithium aluminium hydride in 40 ml of absolute ether, 445 mg of 3(R),7(R),11-trimethyl-dodecanoic acid ethyl ester are heated to boiling for 150 minutes under reflux. The excess lithium aluminium hydride is then decomposed by the dropwise addition of 0.5 ml of water. The mixture is treated with 300 ml of 3-N sulphuric acid and extracted three times with 50 ml of ether each time. The combined ether extracts are washed three times with 20 ml of a 5 wt.% aqueous sodium bicarbonate solution each time and subsequently three times with 30 ml of water each time, dried over magnesium sulphate and evaporated under reduced pressure. The residual 3(R),7(R),11-trimethyl-dodecanol shows the rotation value of $[\alpha]_D^{22} = +2.55$; (c=4.436 in n-octane) after purification by adsorption on 20 g of silica gel [eluant: ether/petroleum ether (30°—60°C) (1:9)].

Example 16.

After conversion into the corresponding magnesium bromide, the optically active C_{10}-alcohol of formula XA obtained according to Example 14 can be condensed in the presence of dilithium tetrachlorocuprate with 5-[2(R),6-benzyloxy - 2,5,7,8 - tetramethyl - 2 - chromanyl]-2(S)-methyl-pentyl-p-toluenesulphonate to give (2R,4'R,8'R)-α-tocopherol-benzyl ether which is transformed by hydrogenation into (2R,4'R,8'R)-α-tocopherol as follows:

A solution of 10 mmol of 3(R),7-dimethyl-octyl-magnesium bromide in 20 ml of anhydrous tetrahydrofuran is treated dropwise while stirring with a solution of 7.7 mmol of 5-[2-(R),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-pentyl-p-toluenesulphonate in 10 ml of tetrahydrofuran. The mixture is cooled to −78°C and, after the addition of 0.4 ml of a 0.1 molar solution of dilithium tetrachlorocuprate [Li_2CuCl_4] in tetrahydrofuran, stirred firstly for 10 minutes at −78°C, then for 2.5 hours at 0°—5°C and subsequently for 17 hours at 23°C. The mixture is then shaken with 1-N aqueous sulphuric acid and extracted with ether. The (2R,4'R,8'R)-α-tocopherol benzyl ether isolated from the ether extract is a viscous oil.

5 mmol of (2R,4'R,8'R)-α-tocopherol benzyl ether are hydrogenated in 50 ml of ethyl acetate under normal conditions with the aid of 1.0 g of palladium/carbon [5:95]. The catalyst is separated after termination of the hydrogen uptake. The filtrate is evaporated under reduced pressure. The residual (2R,4'R,8'R)-α-tocopherol is a colourless viscous oil.

The 5-[2(R),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-pentyl-p-toluenesulphonate used as the starting material herein can be prepared, for example, as follows:

a) 1.0 g of 2(S)-[2'(S)-hydroxy-3(Z)-pentenyl]-2,5,7,8-tetramethyl-6-benzyloxy-chromane are heated together with 2.2 g of dimethylformamide acetal in 10 ml of xylene for 66 hours under reflux at 130°—135°C. The liberated methanol is continuously distilled off. The solution is subsequently evaporated under reduced pressure. The residual brown 5-[2(S),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-N,N-dimethyl-3(E)-pentemide is purified by adsorption on 40 g of silica gel [eluant: ether/petroleum ether (9:1)].

b) The foregoing 5-[2(S),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-N,N-dimethyl-3(E)-pentenamide is hydrogenated with the aid of palladium/carbon [5:95]. The resulting 5-[2(R)-6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-N,N-dimethyl-pentanamide is subsequently heated under reflux for 17 hours in the presence of potassium hydroxide in ethyleneglycol and saponified to give 5-[2(R),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-pentanoic acid.

c) The foregoing 5-[2(R),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-pentanoic acid is reduced in the cold [ice-bath] by treatment with lithium aluminium hydride in dry pyridine to give 5-[2(R),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-pentanol. This alcohol (0.07 mol) is dissolved in 30 ml of dry pyridine. The solution is treated in the cold [ice-bath] with 0.02 mol of p-toluenesulphonyl chloride. The mixture is stirred at 0°C for 20 hours, then

introduced into ice-water and extracted with ether. The 5-[2(R),6-benzyloxy-2,5,7,8-tetramethyl-2-chromanyl]-2(S)-methyl-pentyl-p-toluenesulphonate isolated from the ether extract is a yellow oil.

Example 17.

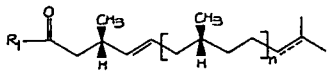
After conversion into the corresponding phosphonium salt, the optically active C_{15}-alcohol of formula XB obtained according to Example 15 can be condensed with 6-acetoxy-2-formyl-2(R),5,7,8-tetramethyl-chromane to give (2R,4'R,8'R)-α-tocopheryl acetate as follows:

6.15 g of 3(R),7(R),11-trimethyl-dodecyl-1-triphenylphosphonium bromide are treated dropwise in absolute dimethoxyethane under nitrogen at room temperature with 12.1 ml of an ethereal lithiumphenyl solution [77 mg/ml]. The mixture is stirred at room temperature for 2 hours, then treated with 1.40 g of 6-acetoxy-2-formyl-2(R),5,7,8-tetramethyl-chromane in 15 ml of dimethoxyethane, heated at 60°C for 3 hours, subsequently cooled in an ice-bath and, after the addition of 50 ml of 1-N sulphuric acid, extracted with ether.

The (2R,4'R,8'R)-1',2'-dehydro-α-tocopheryl acetate (1.19 g) isolated from the ether extract is subsequently hydrogenated under normal conditions in 40 ml of glacial acetic acid with the aid of 120 mg of pre-hydrogenated platinum oxide. After the uptake of 1 mol of hydrogen, the hydrogenation is interrupted. The catalyst is separated. The filtrate is evaporated under reduced pressure. The residual (2R,4'R,8'R)-α-tocopheryl acetate is in a weakly yellow-coloured viscous oil.

WHAT WE CLAIM IS:—

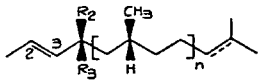
1. Aliphatic carbonyl compounds of the general formula



(I)

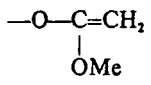
wherein R_1 represents a hydrogen atom or a lower alkoxy, tri(lower alkyl)-silyloxy or di(lower alkyl)amino group, n stands for zero or 1 and the broken line denotes an optional carbon-carbon bond.

2. 3(S),7-Dimethyl-4(trans)-octen-1-oic acid ethyl ester.
3. 3(S),7-Dimethyl-4(trans)-octen-1-oic acid dimethylamide.
4. 3(S),7-Dimethyl-4(trans)-octen-1-al.
5. 3(S),7-Dimethyl-4(trans)-octen-1-oic acid.
6. 3(S),7(R),11-Trimethyl-4(trans),10-dodecadien-1-oic acid ethyl ester.
7. A process for the manufacture of the aliphatic carbonyl compounds of formula I given in claim 1, which process comprises reacting a pure optically active isomer [free from other optically active isomers] of the general formula

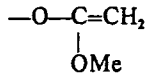


(II)

wherein n and the dotted line have the significance given in claim 1 and one of R_2 and R_3 represents a hydrogen atom and the other represents the hydroxy group or the



group [Me = alkali metal]; the 2,3-double bond having the cis-configuration when R_2 represents the hydroxy group or the



group and having the trans-configuration when R_2 represents a hydrogen atom,

with an orthoacetic acid ester of the formula $H_3C—C(OR_4)_3$ [R_4 = lower alkyl], a ketalised N-dialkyl-acetamide of the formula

$$H_3C—\underset{\displaystyle N(R_4)_2}{\underset{|}{C}}(OR_4)_2,$$

an alkoxy-vinyl-dialkylamine of the formula

$$H_2C=\underset{\displaystyle OR_4}{\underset{|}{C}}—N(R_4)_2$$

or an alkyl-vinyl ether of the formula $H_2C=CH—OR_4$ when R_2 or R_3 represents the hydroxy group; or with a trialkyl-silyl halide of the formula $XSi(R_4)_3$ [X = halogen] when R_2 or R_3 represents the

$$—O—\underset{\displaystyle OMe}{\underset{|}{C}}=CH_2$$

group, and subjecting the intermediate obtained to a Claisen rearrangement.

8. A process according to claim 7 wherein the reaction is carried out using orthoacetic acid ethyl ester.

9. A process according to claim 7, wherein the reaction is carried out using 1-dimethylamino-1,1-dimethoxyethane.

10. A process according to claim 7, wherein the reaction is carried out using ethyl-vinyl ether.

11. A process according to claim 7, wherein the reaction is carried out using tert.-butyl-dimethyl-silyl chloride.

12. A process according to claim 7 and claim 8, wherein 6-methyl-2(cis)-hepten-4(R)-ol or 6-methyl-2(trans)-heptan-4(S)-ol is reacted to give 3(S),7-dimethyl-4(trans)-octen-1-oic acid ethyl ester.

13. A process according to claim 7 and claim 9, wherein 6-methyl-2-(cis)-hepten-4(R)-ol or 6-methyl-2(trans)-hepten-4(S)-ol is reacted to give 3(S),7-dimethyl-4(trans)-octen-1-oic acid dimethylamide.

14. A process according to claim 7 and claim 10, wherein 6-methyl-2(cis)-hepten-4(R)-ol or 6-methyl-2(trans)-hepten-4(S)-ol is reacted to give 3(S),7-dimethyl-4(trans)-octen-1-al.

15. A process according to claim 7 and claim 11, wherein the lithium enolate of 6-methyl-2(cis)-hepten-4(R)-ol acetate or the lithium enolate of 6-methyl-2(trans)-hepten-4(S)-ol acetate is reacted to give 3(S),7-dimethyl-4(trans)-octen-1-oic acid tert.-butyl-dimethyl-silyl ester.

16. A process according to claim 7 and claim 8, wherein 6(R),10-dimethyl-2(cis),9-undecadien-4(R)-ol or 6(R),10-dimethyl-2(trans),9-undecadien-4(s)-ol is reacted to give 3(S),7(R),11-trimethyl-4(trans),10-dodecadien-1-oic acid ethyl ester.

17. A process according to claim 7 and claim 8, wherein 6(R),10-dimethyl-2(cis)-undecen-4(R)-ol or 6(R),10-dimethyl-2(trans)-undecen-4(S)-ol is reacted to give 3(S),7(R),11-trimethyl-4(trans)-dodecen-1-oic acid ethyl ester.

18. A process according to claim 7 and claim 9, wherein 6(R),10-dimethyl-2(cis)-undecen-4(R)-ol or 6(R),10-dimethyl-2(trans)-undecen-4(S)-ol is reacted to give 3(S),7(R),11-trimethyl-4(trans)-dodecen-1-oic acid dimethylamide.

19. A process for the manufacture of the aliphatic carbonyl compounds of formula I given in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 13.

20. An aliphatic carbonyl compound of formula I given in claim 1, when manufactured by the process claimed in any one of claims 7 to 19 inclusive.

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